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ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
03/01/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	09/809,029	BARNARDO ET AL.	
	Examiner	Art Unit	
	GARY W. COUNTS	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,11-17,20,24-27 and 30-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,11-17,20,24-27 and 30-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/01/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

1. The amendment filed 11/30/09 is acknowledged and has been entered. Currently, claims 1-3, 5-7, 11-17, 20, 24-27 and 30-42 are pending and under examination.

Withdrawn Rejections

2. All objections and rejections of claims not reiterated herein, have been withdrawn.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-3, 5-7 and 11-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty (US 5,292,641) in view of Tidey et al (US 6,046,013) and further in view of Chang et al (US 5,270,169) and Walter et al. (International Immunology, Vol. 9, p. 451-459, 1997) or Baserga et al (US 6,218,363).

Pouletty disclose a method of detecting and identifying antibodies to HLA alleles bound (immobilized) to a support (e.g. abstract, col 1- col3). Pouletty discloses that the method can be used to detect antibodies to the alleles of interest (col 3). Pouletty discloses that the HLA allele of interest can be Class I or Class II (col 3). Pouletty discloses that the antigens can be derived from any convenient source of the desired antigen repertoire (col 3, lines 22-30). Pouletty disclose contacting a sample such as serum, plasma saliva, or cerebrospinal fluid (body fluids) to detect the antibodies in the sample (e.g. col 2 – col 4). Pouletty et al disclose that the detection of antibody bound to the HLA antigen can be determined by utilizing a labeled antibody (col 4, lines 37-68). Pouletty discloses that the label can be enzymes, radioisotopes, biotin to bind to labeled avidin (col 4). Pouletty also discloses that the detection can be by ELISA, FIA or RIA (col 4). Pouletty discloses that a panel of HLA antigens can be used to detect the

antibodies (e.g. col 2). Pouletty discloses that the reagents can be packaged into a kit (col 5). Pouletty discloses that the support can be a bead, microtiter plate or nitrocellulose (col 3). Pouletty et al disclose the assay can take less than three hours (col 6, lines 13-40).

Pouletty et al differs from the instant invention in failing to teach the HLA antigens are immobilized to discrete sites of the solid support.

Tidey et al discloses methods for detecting and identifying antibodies in a sample (e.g. abstract, col 2). Tidey et al discloses that HLA antigens which are unique from each other and separated from each other on a solid support are used to detect the antibodies (e.g. col 2 - col 4). Tidey et al discloses that HLA antigens can have specific alleles which bind to antibodies (e.g. col 4). Tidey et al discloses that 40 different HLA molecules can be immobilized to the solid support at different locations (col 4, lines 65-67). Tidey et al discloses that the separation of different HLA molecules provides for an infinite number of grades of antibody reactions which can be assigned, making it much easier to sort and identify the antibodies (e.g. col 12) and also teaches that it provides alternative techniques which can be performed simply, can be automated, provides a readily discernible result which is significant for the prognosis of transplant acceptance, and are comparable to data from existing tests. (col 2, lines 23-27). Tidey et al also discloses packaging components into a kit.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate different HLA antigens at separate locations of the support of Pouletty because Pouletty specifically teaches that a panel of antigens can

be used and Tidey et al shows that using different HLA antigens at different locations of a support provides for an infinite number of grades of antibody reactions which can be assigned, making it much easier to sort and identify the antibodies and also teaches that it provides alternative techniques which can be performed simply, can be automated, provides a readily discernible result which is significant for the prognosis of transplant acceptance, and are comparable to data from existing tests.

Pouletty and Tidey et al fail to teach the use of recombinant MHC or HLA molecules.

Chang et al teaches that it is known in the art that synthetic HLA antigens which mimic the antigenic reactivity of HLA epitopes are equivalent to HLA antigens for the detection of specific antibodies in a biological sample (col 3, lines 48-62). Chang et al teaches that the detection of the antibodies can be of antibodies to at least one HLA allele (col 2, lines 15-20). Chang et al also teaches HLA molecules can be attached to solid supports such as a microtiter plate, beads or nitrocellulose (col 3, lines 1-19).

Walter et al discloses that recombinant HLA molecules can be used to detect antibodies in a sample. Walter et al., disclose detecting a monoclonal PA2.1 antibodies (specific for HLA-A2 and A28). Walter et al disclose that this antibody binds to recombinant HLA-A2 peptide complexes. Walter et al disclose detecting the PA2.1 antibodies bound to the A2 complex with goat anti-mouse Ig conjugated to horseradish peroxidase (p. 452). Walter et al disclose that the HLA-A2 molecule is produced in E.Coli (prokaryotic expression system) (p. 451). Walter et al disclose the recombinant molecule can be immobilized and bound by antibody (p. 456, first column, lines 43 –

53). Walter et al disclose assembling the HLA-A2 (HLA-A*001) heavy chain and B_2-microglobuling in the presence of a peptide from gag protein (Gag, amino acids 77086, SLYNTVATL) (It is noted that this recombinant molecule appears to be the same recombinant molecule as disclosed by applicant (see page 23, Table 1). Walter et al disclose labeled antibodies that bind to the PA2.1 antibodies. Walter et al teaches that the recombinant complexes contain native epitopes, consistent with the presence of correctly folded molecular complexes (p.456, 2nd col).

Baserga et al also disclose that MHC or HLA Class I molecules can be produced by recombinant DNA techniques. Baserga et al disclose that the recombinant MHC or HLA Class I molecule is produced in the host by expression. The transformed host may be a prokaryotic or eukaryotic cell. (col 14, lines 1-21). These recombinant molecules retain the therapeutic or diagnostic activity of the naturally occurring molecule and provides methods of identifying MHC Class I peptides.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate recombinant HLA antigens such as taught by Walter et al or Baserga et al into the modified method of Pouletty because Chang et al teaches that it is known in the art of detecting HLA antibodies that a synthetic HLA antigen can be substituted as an equivalent reagent for HLA antigens for the purpose of detecting HLA antibodies and Walter shows that recombinant HLA antigens can be used to detect allele specific antibodies and that the recombinant complexes contain native epitopes, consistent with the presence of correctly folded molecular complexes. Baserga et al also shows that it is known in the art that recombinant HLA molecules retain the

therapeutic or diagnostic activity of the naturally occurring molecule and provides methods of identifying MHC class I peptides. Therefore, one of ordinary skill would have a reasonable expectation of success incorporating recombinant HLA antigens as taught by Walter et al or Baserga et al into the modified method of Pouletty.

7. Claims 20, 24, and 30-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty, Tidey et al., Chang et al., Walter et al and Baserga et al as applied to claims 1-3, 5-7 and 11-17 above, and further in view of Boguslaski et al (US 5,420,016).

See above for the teachings of Pouletty, Tidey et al., Chang et al., Walter et al and Baserga et al.

Pouletty, Tidey et al., Chang et al., Walter et al and Baserga et al. differ from the instant invention in failing to teach all of the components packaged into a kit.

Boguslaski et al disclose assembling various system components into a test kit. By assembling these components into test kits, it makes it more convenient and facile for the test operator (col 7, lines 8-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to assemble the various components of the modified method of Pouletty into kits such as taught by Boguslaski et al because Pouletty teaches the use of kits and Boguslaski shows that test kits make it more convenient and facile for the test operator. Therefore, one of ordinary skill in the art would have been motivated to include the components of the modified method of Pouletty into a kit.

With respect to the number of MHC alleles represented as currently recited in the claims. The modified method of Pouletty teaches 40 different HLA molecules which have distinct alleles. Further, the optimum number of MHC alleles to be represented can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation ." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272,276, 205 USPQ 215, 218-219 (C.C.P.A. 1980).

8. Claims 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty, Tidey et al., Chang et al., Walter et al., Baserga et al and Boguslaski et al as applied to claims 1-3, 5-7, 11-17, 20, 24, and 30-42 above, and further in view of Luxembourg et al.

See above for the teachings of Pouletty, Tidey et al., Chang et al., Walter et al., Baserga et al and Boguslaski et al.

Pouletty, Tidey et al., Chang et al., Walter et al., Baserga et al. and Boguslaski et al differ from the instant invention in failing to teach the MHC or HLA molecule is fused to biotin.

Luxembourg et al disclose recombinant MHC molecules which are biotinylated (page 3, paragraph 0018, & page 4, paragraph 0027). Luxembourg et al disclose that these recombinant MHC molecules are biotinlyated to provide attachment to solid support coated with avidin. Luxemburg et al disclose that the use of this avidin-biotin system provides for the isolation of peptides such as antibodies (p. 5, paragraphs 0030, and 0031).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an avidin-biotin system as taught by Luxembourg et al into the modified method of Pouletty because Luxembourg et al shows that the use of this avidin-biotin system provides for the isolation of peptides such as antibodies. Further, the use of avidin-biotin systems to immobilize and capture reagents is very well known in the art. Therefore, one of ordinary skill in the art would have a reasonable expectation of success incorporating avidin-biotin as taught by Luxembourg et al into the modified method of Pouletty.

Response to Arguments

9. Applicant's arguments filed 11/30/09 have been fully considered but they are not persuasive.

103 Rejections

Applicant argues that claims 1 and 2 have been amended to include recitation of, "…wherein antibodies directed to each allele, if present in the sample, are separately detected and identified in less than three hours". Applicant further argues that each of Pouletty et al (col 6), Tidey et al (col 8) and Chang et al (Experimental col 5, bridging col. 6) require an overnight incubation with antigen or antibody to secure binding of the material to the solid support. These arguments are not found persuasive because a review of Pouletty et al col 6 , lines 1-10 indicates that the overnight incubation is directed to the preparation of the plate to be used in the assay and is not directed to the running time of the assay. The actual assay performed in Pouletty in col 6, lines 13-15 discloses mixing serum with antigen and incubating for 15 minutes, then adding the mixture to an HLA-coated plate and incubate for 4 minutes (total of these two steps would be 19 minutes). Pouletty et al then discloses adding conjugate and incubating for 30 minutes (col 6, lines 31-34) (19 minutes from the previous two incubation steps plus the 30 minutes would total 49 minutes). Pouletty et al then discloses the addition of substrate and incubation for five minutes (col 6, lines 35-38), stop and read results (col 6, lines 39-40) (49 minutes from the previous incubations plus the 5 minutes would total 54 minutes for the running of the assay). Thus, Pouletty et al teaches performing the assay in less than 3 hours. With respect to Applicant's arguments directed to Tidey et al and Chang et al as teaching overnight incubations. These arguments are irrelevant because the Examiner has not relied upon the teachings of Tidey et al and Chang et al for the method steps but rather has relied upon Tidey for teaching the use of different HLA antigens at different locations of a solid support and the incorporation of different

HLA antigens at separate locations of the support (see rejections above) in the method of Pouletty et al. Further, the Examiner has not relied upon Chang et al for teaching the method steps but rather has relied upon Chang et al for teaching that it is known in the art that synthetic HLA antigens which mimic the antigenic reactivity of HLA epitopes are equivalent to HLA antigens for the detection of specific antibodies in a biological sample (see rejections above directed to the combination of Chang with the other references).

Applicant further argues that the claimed methods can be performed in just 30 minutes for immobilizing the HLA monomer to the solid support. This argument is not found persuasive because In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., 30 minutes for immobilizing the HLA monomer to the solid support) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The instant claims do not recite a step of immobilizing the HLA monomer to a solid support. Further, it is noted that claims 1 or 2 do not even recite a monomer but merely recite immobilized recombinant MHC or HLA.

Applicant argues that neither Walter et al nor Baserga et al cure the deficiencies of Pouletty et al in view of Tidey et al. Applicant states that neither Walter et al nor Baserga et al teach a method for detecting anti-HLA antibodies in lest than three hours. This is not found persuasive because of reasons stated above that Pouletty et al teach the assay is less than three hours. Therefore, the combination of Pouletty et al., Tidey

et al., Chang et al., Walter et al., and Baserga et al are considered appropriate and read on the instantly recited claims.

Applicant argues that Boguslaski et al does not cure the deficiencies of Pouletty in view of Tidey et al., and further in view of Chang et al and Walter et al and Baserga et al. Applicant states that Boguslaski et al does not teach a method or kit wherein the detection occurs in less than three hours. These arguments are not found persuasive because of reasons stated above. Further, with respect to the kit as instantly recited the combination of references teach the same structural limitations as instantly recited and therefore the kit of the combination of Pouletty in view of Tidey et al., and further in view of Chang et al and Walter et al and Baserga et al. would detect and identify the antibodies in less than three hours.

Applicant argues that Luxembourg et al does not cure the deficiencies of Pouletty in view of Tidey and further in view of Chang et al., Walter et al., Baserga et al. and Boguslaski e al. Applicant states that Luxembourg et al does not teach a method wherein the detection occurs in less than three hours. This argument is not found persuasive because of reasons stated above that Pouletty et al teach the assay is less than three hours. Therefore, the combination of Pouletty et al., Tidey et al., Chang et al., Walter et al., Baserga et al and Boguslaski e al are considered appropriate and read on the instantly recited claims.

Conclusion

10. No claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GARY W. COUNTS whose telephone number is (571)272-0817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ Gary W. Counts/
Examiner, Art Unit 1641

/Melanie Yu/
Primary Examiner, Art Unit 1641